The interplay between the genome and the exposome in psychosis spectrum

12.2 Summary

In **Chapter 2**, the longitudinal risk for the incidence of clinical psychosis was assesses in a general population sample in relation to preceding psychosis risk states and DSM-IV diagnoses of non-psychotic mental disorders (mood disorders, anxiety disorders, alcohol use disorders, and drug use disorders). Estimated hazard ratio suggested that mood disorders, drug use disorders, and psychosis high-risk state are important determinants for increased risk for clinical psychosis. However, given the low prevalence of the high-risk state, the fraction that could be prevented if the high-risk state was eliminated (population attributable fraction) was comparatively low. Successful psychosis prevention approaches might benefit from focusing on broad psychopathology.

In **Chapter 3**, I evaluated to what degree the association between risk factors commonly associated with psychosis spectrum disorder (PSD; i.e. environmental and proxy genetic factors) and psychosis expression in the general population is contingent on the presence of other dimensions of psychopathology (i.e. affective dysregulation, negative symptoms, and cognitive alterations). The results show a dose-response relationship between risk factors associated with PSD and psychosis expression, with greater odds for psychosis expression being associated with the exposure to a greater number of risk factors. Furthermore, in support of the multidimensional approach, the effect that risk factors had on PE was contingent on the presence of the other symptom dimensions, especially affective dysregulation.

In **Chapter 4,** I introduce one of the epidemiological datasets that were used in this dissertation. The TwinssCan project is a longitudinal general population twin cohort, which recruited from the East Flanders Prospective Twin Survey. The review highlights important findings on the contribution of environmental and genetic factors on subclinical expression of psychosis and affective phenotypes, focusing on macro (e.g. monthly) as well as micro (e.g. momentary) level psychopathological changes. Furthermore, applying novel experimental tools, studies conducted in this cohort evaluated the role of neurocognitive processes such as salience attribution and sensitivity to social defeat in the pathway to mental ill health.

In **Chapter 5**, one of the studies conducted in the TwinssCan sample is presented. Possible due to different methodological approaches, previous studies found inconsistent results on whether speech illusions during the white noise task are associated with subclinical expression of psychotic symptoms in the general population. Therefore, I tested the association between speech illusion and measurements for subclinical expression of psychotic symptoms following two different approaches. The results suggest, that contrary to findings derived from clinical

samples, speech illusion during the white noise task are not associated with subclinical expression of psychotic symptoms in the general population.

Chapter 6 presents a study testing polygenic risk score for schizophrenia (PRS-SCZ) for an interaction with early and late stressors (childhood adversity and minor daily-life stressors) in association with dynamic pluripotent mental processes in the largest ever EMA data collected from the TwinssCan project. The study provided evidence that childhood adversity and early lifetime stressors pleiotropically affect emotional dysregulation and subtle psychosis expression in daily life. Furthermore, while PRS-SCZ does not interact with daily-life stressors, it interacts with childhood adversity on pluripotent psychopathology. The findings help to understand person-specific effects of the complex interactions between environmental and genetic factors on nonspecific health outcomes.

In **Chapter 7** the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia was tested in a large international case-control cohort with patients diagnosed with schizophrenia. Several environmental exposures, as well as polygenic risk score for schizophrenia, were associated with case-status. The study indicated a positive additive interaction between PRS-SCZ and several environmental exposures (i.e. lifetime regular cannabis use and early-life adversities; sexual abuse, emotional abuse, emotional neglect, and bullying). The findings suggest that some individuals may only develop a diagnosis of schizophrenia if both the genetic and nongenetic exposures (i.e. emotional and sexual abuse) are present.

In **Chapter 8** the exposome score for schizophrenia (an aggregate score of environmental liability for schizophrenia) was for the first time estimated and validated by means of predictive modeling approach in two large independent datasets. Exposome scores for schizophrenia were estimated using different models; logistic regression, Gaussian Naïve Bayes, the LASSO and Ridge penalized classification models. Additionally, an exposome score based on meta-analyses and a simple sum-score of exposures were estimated. The findings demonstrate that a simple score based on logistic regression, which takes into account of the dependent effect of various exposures, is best equipped to assess environmental liability for schizophrenia in an independent test dataset. The exposome score for schizophrenia significantly differentiated between cases, unaffected siblings, and healthy controls in the independent test sample.

Chapter 9 tested whether recent stressful life events interacted with indicators of genetic liability, polygenic risk score for schizophrenia, and environmental liability, exposome score

for schizophrenia on health outcome in the general population. Genetic and environmental liability was associated with poorer health outcomes, especially mental health. The exposome score moderated the association of recent stressful life events with mental and physical health, while polygenic risk did not. The results were confirmed by several sensitivity analyses.

Chapter 10 investigated the contribution of the polygenic risk score and the exposome score for schizophrenia to psychosis expression across the spectrum. Genomic and exposomic liability were associated with a diagnosis of schizophrenia and schizotypy in healthy controls and unaffected siblings. Furthermore, genomic liability moderated the effect of exposomic liability on case-status and schizotypy in healthy controls and unaffected siblings. The results support the conceptual framework of an etiological continuity across psychosis spectrum.